

Remarks

Claims 1-3 and 5-19 are pending.

Claim 4 and 20-47 have been canceled. Applicants retain the right to pursue the subject matter of these claims in other patent applications.

Claim 1 has been amended by the addition of the subject matter of canceled claim 4. Support for the amendment is also found in the specification on page 8, line 21 to page 9, line 11.

Claim 5 has been amended to change its dependency to claim 1.

New claims 48-50 have been introduced. Support for these claims are found in the specification on page 8, lines 11-20.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 11 and 12 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention with respect to the microorganisms. The Examiner has indicated that the rejections under 35 U.S.C. §112, first paragraph, will be withdrawn upon receipt of a statement pertaining to the availability of the strain.

Accordingly, Applicants submit herewith a copy of a Deposit Certificate from the ATCC that indicates that *Sorangium cellulosum* SC16408 and *Sorangium cellulosum* SC16449 were deposited with the ATCC under the terms of the Budapest Treaty and were given the accession numbers of PTA-3880 and PTA-3881, respectively.

Since the deposit of PTA-3880 and PTA-3881 were made with the ATCC under the Budapest Treaty, as evidenced by the attached certificate, it is respectfully requested that this rejection be withdrawn.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claim 5 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 has been amended to change its dependency to claim 1. In the previous amendment, dated March 21, 2006, the numeral "4" was deleted from Claim 4 by a strike-through the number. The Applicants acknowledge the difficulty of discerning the deletion of the numeral "4" using a

strike-through the number "4". In the present amendment, Applicants have deleted the numeral "4" using double brackets.

Rejections Under 35 U.S.C. §102(e)

Claims 1-19 stand rejected under 35 U.S.C. 102(e) as anticipated by US 6,921,650 to Julien et al. (henceforth "Julien"). According to the Examiner, the reference discloses each of the process steps in claims 1-19. However, the Examiner has not cited the particular part of the reference that he relied upon for this rejection. According to 37 CFR 1.104(c)(2):

"In rejecting claims for want of novelty or for obviousness, the examiner must cite the best references at his or her command. When a reference is complex or shows or describes inventions other than that claimed by the applicant, the particular part relied on must be designated as nearly as practicable. The pertinence of each reference, if not apparent, must be clearly explained and each rejected claim specified."

Applicants respectfully assert that the cited reference, which contains over 100 pages, is both complex and describes inventions other than that claimed in the present application. Since the Examiner has not stated the particular part(s) relied upon for the present rejections, the Applicants have based their response on the particular sections of the reference that they believe are pertinent to the present rejections. Applicants respectfully request that in future office actions, the Examiner states the particular part(s) of the reference relied upon for the rejection. This will facilitate prosecution of the patent application, allow the Applicants to respond directly and concisely to the rejections, as well as serving public policy by not unduly increasing the time and cost of prosecuting the application.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicants respectfully point out that the cited reference does not disclose each and every element of the claimed invention.

Claim 1 is directed towards a process comprising the steps of:

- (a) fermenting a strain of epothilone-producing microorganism in the presence of a resin that absorbs epothilone B by hydrophobic interaction;
- and
- (d) crystallizing epothilone B from the extraction phase,

as well as other steps.

Example 7 in Julien discloses a fermentation process to prepare epothilones C and D without epothilones A and B (col. 129, lines 16-24). Column 129, line 51 to column 131, line 29 discloses details of this fermentation process. Column 131, lines 31-52 discloses extraction and analysis of the prepared compounds (col. 131, lines 30-52) with further reference to extraction and analysis steps in example 4 (col. 120, lines 14-45). In Example 7, Julien does not disclose a process for the preparation of epothilone B. Nor does Julien disclose the step of crystallizing an epothilone, in particular, crystallizing epothilone B, and more particular, crystallizing epothilone B from the extraction phase.

Examples 4 and 5 in Julien disclose preparation of epothilone B. However, Examples 4 and 5 do not disclose preparation of epothilone B in the presence of a resin and further, does not disclose crystallization of the epothilone B.

As such, Julien does not disclose each and every step of the invention as claimed in independent claim 1 and dependent claims 2-3 and 5-19. Applicants request withdrawal of the rejection over claims 1-3 and 5-19 under 35 U.S.C. 102(e).

Rejections Under 35 U.S.C. §103(a)

Claims 1-19 stand rejected under 35 U.S.C. 103(a) as obvious in view of US 6,921,650 to Julien et al.

The examiner has made general assertions regarding the substitutions of microorganisms, solvents, reagents, and additives, but has not cited any particular passages in Julien to support his rejection. Applicants are responding to this rejection primarily based on the disclosures of Example 4-5 and 7 in Julien, which describe processes to prepare specific epothilones. Examples 4 and 5 disclose production of epothilone B. Example 7 discloses the preparation of epothilones C and D, employing a strain that produce only epothilones C and D without epothilones A and B. (col. 129, lines 20-23). Also, Example 3 discloses the construction of a bacterial artificial chromosome for expression of epothilone and states in the future tense for one strain, "This strain will be fermented and tested for the production of epothilones A and B." (col. 115, lines 6-7) and states in the present tense for a second strain, "This strain is fermented and tested for the production of epothilones A and B." (col. 115, lines 6-7 and lines 26-28). However, the example does not disclose actual or intended fermentation and extraction conditions. The Applicants respectfully request the Examiner to point out if other disclosures in this reference were employed in the present rejection.

Three basic criteria must be met to establish a *prima facie* case of obviousness:

- There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.
- There must be a reasonable expectation of success.
- The prior art reference must teach or suggest all the claim limitations.

Claim 1 of the present invention is directed towards a process, which provides improved concentrations of epothilone B relative to epothilone A. The claimed process includes specific steps for fermenting and isolating epothilone B, including the step of crystallizing epothilone B. As discussed above, Julien does not disclose, teach, or suggest the step of crystallizing an epothilone, in particular, crystallizing epothilone B, and more particular, crystallizing epothilone B from the extraction phase, as claimed in claim 1 of the present invention. Therefore, a *prima facie* case of obviousness has not been established since the cited reference does not teach or suggest all the claim limitations.

Further, Applicants assert that the Examiner has engaged in hindsight reconstruction by employing the disclosure of the present specification as a template to pick and choose specific details from Julien to reconstruct the process of claims 1-3 and 5-19 of the present invention.

Example 4 discloses the preparation of plates of cells containing the same media as Julien's production culture with propionate (col. 120, lines 4-13). However, fermentation in the presence of resin is not disclosed in this example. Nor does this example disclose, teach, or suggest crystallization of the epothilone B or another epothilone. It should also be noted that in this example, Julien discloses "In some cultures, it was observed that the absence of propionate increased the proportion of epothilone B to epothilone A." This teaching would certainly dissuade one with ordinary skill in the art against adding an additive such as propionate to a fermentation process to produce epothilone B, especially to increase the ratio of epothilone B to epothilone A as claimed in claimed 1, and thus effectively teaches one with ordinary skill in the art against the use of propionate in a fermentation process to produce epothilone B.

Example 5 discloses the conversion of epothilone D to epothilone B using a fusion protein (col. 123, lines 16-20). The disclosed conversion process does not include the step of fermenting a strain of epothilone-producing microorganism in the presence of a resin, as well as other steps of claim 1, such as crystallizing epothilone B.

Example 7 teaches the preparation of epothilones C and D, employing a strain that produce only epothilones C and D without epothilones A and B. (col. 129, lines 20-23). Several different fermentation processes are described in this example, including a 5L bioreactor process using resin. The example does not disclose, teach, or suggest the preparation of epothilone B, and in particular, a step for crystallizing epothilone B.

Applicants respectfully contend that the Examiner is picking and choosing particular steps and particular additives from the various processes disclosed in Julien, in particular from those disclosed in Examples 4-5 and 7. No motivation or suggestion has been provided in either the cited reference or in the knowledge generally available to one with ordinary skill in the art to pick a step of fermentation in the presence of a resin from the 5L bioreactor process to prepare epothilone C and epothilone D in the absence of epothilone A and epothilone B (Example 7) and pick a process to prepare plate cells, wherein the production culture contained propionate (Example 4), especially since Example 4 teaches that in some cultures, the absence of propionate increased the proportion of epothilone B to epothilone A. Numerous solvents, reagents, and additives employed in the fermentation and extractions processes are disclosed in Julien. However, no motivation or guidance is provided to selected particular ones from the various disclosed processes. Although one may assert that it is obvious to try particular solvents, reagents, or additives, such an assertion does not meet the standard to establish a *prima facie* case of obviousness.

In summary, the Applicants assert that a *prima facie* case of obviousness has not been established. First, Julien does not teach or suggest all the claim limitations of the amended claim 1 and dependent claims 2-3 and 5-19. Second, hindsight reconstruction was employed to pick and choose certain elements from Julien to reconstruct the present invention. Applicants respectfully request withdrawal of the rejection over claims 1-3 and 5-19 under 35 U.S.C. 103(a).

Conclusion

It is believed that all rejections of the claims have been fully addressed. The Examiner is invited to contact the undersigned if it is believed a telephonic communication would expedite the prosecution of this application.

In the event that the Commissioner determines any extra fee to be due, please charge any necessary additional fees (or credit any overpayment) to the Assignee's Deposit Account No. 19-3880.

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000

Date: *July 24, 2006*

Gary Greenblatt

Gary D. Greenblatt
Agent for Applicant
Reg. No. 47,609
Phone: 609-252-3850

**BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE**



INTERNATIONAL FORM

**RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2**

To: (Name and Address of Depositor or Attorney)

Bristol-Myers Squibb Company
Attn: Stephen B. Davis
P.O. Box 4000
Princeton, NJ 08543-4000

Deposited on Behalf of: Bristol-Myers Squibb Company

Identification Reference by Depositor:

Sorangium cellulosum: SC16408
Sorangium cellulosum: SC16449

Patent Deposit Designation

PTA-3880
PTA-3881

The deposits were accompanied by: a scientific description a proposed taxonomic description indicated above. The deposits were received November 27, 2001 by this International Depository Authority and have been accepted.

AT YOUR REQUEST: We will inform you of requests for the strains for 30 years.

The strains will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strains, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strains.

If the cultures should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace them with living cultures of the same.

The strains will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the cultures cited above was tested December 17, 2001. On that date, the cultures were viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA.

Signature of person having authority to represent ATCC:



Tanya Nunnally, Patent Specialist, Patent Depository

Date: December 27, 2001

cc: Timothy J. Babcock
(Ref: Docket or Case No.: LD0283)